# Newer Diabetes Medications, TZDs, and Combinations

Key Questions and Inclusion Criteria

## Key Questions

1. What is the comparative efficacy and effectiveness of newer diabetes medications, TZDs, and combination products (used as combination products or dual therapy) for children and adults with diabetes mellitus?

2. What is the comparative tolerability and frequency of adverse events for newer diabetes medications, TZDs, and combination products (used as combination products or dual therapy)?

3. Are there subgroups of patients based on demographics (age, racial groups, gender), comorbidities (drug-disease interactions, obesity), or other medications (drug-drug interactions) for which newer diabetes medications, TZDs, and combination products (used as combination products or dual therapy) differ in efficacy/effectiveness or frequency of adverse events?

## Inclusion Criteria

Populations

- Adults and children with type 2 diabetes for all included medications
- Adults and children with type 1 diabetes for Pramlintide (Symlin®) only
- Excluded populations: gestational diabetes

Interventions

"Newer diabetes medications" refer to Amylin agonists, DPP-4 inhibitors, and GLP-1 analogues

| Class | Generic Name | Trade Name | Forms |
|---|---|---|---|
| Amylin agonists | Pramlintide* | Symlin® | Injectable |
| DPP-4 Inhibitors | Sitagliptin<br>Saxagliptin | Januvia®<br>Onglyza® | Oral tablet<br>Oral tablet |
| GLP-1 analogues (Incretin mimetics) | Exenatide* | Byetta® | Injectable |
| Thiazolidinediones (TZDs) | Pioglitazone<br>Rosiglitazone | Actos®<br>Avandia® | Oral tablet<br>Oral tablet |
| Fixed Dose Combination Products (FDCPs)** | Metformin + Rosiglitazone<br>Metformin + Pioglitazone<br>Glimepiride + Rosiglitazone<br>Glimepiride + Pioglitazone<br>Metformin + Sitagliptin<br>Metformin + Glyburide<br>Metformin + Glipizide | Avandamet®<br>Actoplus Met®*<br>Avandaryl®<br>Duetact®*<br>Janumet®<br>Glucovance®<br>Metaglip® | Oral tablet<br>Oral tablet<br>Oral tablet<br>Oral tablet<br>Oral tablet<br>Oral tablet<br>Oral tablet |

*Not available in Canada

**the FDCPs or the individual components of those FDCPs used together but in separate pills (aka dual therapy) will both be included in the review

Comparators:

- For "newer diabetes medications" (pramlintide, sitagliptin, saxagliptin, and exanetide): within class: comparing any one of these to another one, between class: any one of these vs. (1) placebo, (2) other hypoglycemic agents
- For TZDs: within class: pioglitazone vs. rosiglitazone, between class: pioglitazone or rosiglitazone vs. (1) placebo, (2) other hypoglycemic agents
- For combination products listed above:
  - combination therapy (2 meds in 1 pill) vs. monotherapy with one of the components of the combination therapy
  - dual therapy (2 meds in separate pills) vs. monotherapy with one of the components of the dual therapy

- "Other hypoglycemic agents" include the following: insulin, 2nd generation sulfonylureas and beyond, metformin, meglitanides, TZDs, alpha-glucosidase inhibitors, fixed-dose combination products
- Between class comparisons require 1 or more groups receiving a medication in the class of interest and 1 or more groups not receiving a medication in the class of interest (eg. 1 or more groups receiving a TZD and 1 or more not receiving a TZD)

Efficacy and effectiveness outcomes

- Intermediate outcomes:
  1. Hemoglobin A1c
  2. Change in weight for pramlintide, sitagliptin, saxagliptin, and exanetide

- Health outcomes:
  1. Microvascular disease: chronic kidney disease, including renal dialysis, renal transplantation, end-stage renal disease; retinopathy including proliferative retinopathy and blindness; peripheral neuropathy
  2. Macrovascular disease: cardiovascular events, cardiovascular mortality, stroke/TIA, coronary heart disease, cardiovascular procedures, extremity amputation
  3. Lower extremity ulcers
  4. All-cause mortality
  5. Quality of life
- Utilization outcomes:
  1. Hospitalization and medical visits related to diabetes care

Harms/Adverse Events outcomes

- Overall adverse events
- Withdrawals due to adverse events
- Major adverse events (including diabetic ketoacidosis, non-ketotic hyperosmolar coma)
- Specific adverse events (including cancers/neoplasms, infections, hypoglycemia, liver toxicity, liver function abnormalities, gastrointestinal effects, adverse changes in lipid concentrations, weight gain)

Study designs

• For intermediate outcomes,
    1) randomized controlled trials
    2) good-quality systematic reviews
• For health and utilization outcomes:
    1) In addition to the above, observational studies will be included if they are cohort studies with a comparison group or case-control studies
• For harms:
    1) randomized controlled trials, controlled clinical trials
    2) good-quality systematic reviews
    3) population-based comparative cohort studies focused on adverse events, case-control studies, reports from voluntary adverse event reporting systems

Duration:

For all study designs and all key questions ≥ 12 weeks

Sample size:

Any size